Role of Cell Cycle checkpoints in cell division regulation

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Abstract- Cell cycle is the regulatory mechanism of regulated cell division process in the body. The cell cycle checkpoints such as regulatory protein and genes work together in different stages during period of the cell cycle known as interphase that regulates the cell division in regulatory manner. Some of the regulatory proteins and gene such as p53, CDK family, cyclin family MAPK etc. responsible for proper functioning of the cell division processes things like DNA parts that haven't been copied stop the cell cycle from moving forward, DNA replication, cell growth, growth factors, cell proliferation, differentiation etc. in both the cells prokaryotic as well as eukaryotic cell. The CDKIs are often changed or turned off in many types of human cancer. Normal genes that have the potential to mutate into oncogenes are known as proto-oncogenes. A gene that develops a function or is overexpressed and transforms a healthy cell into a cancerous one is called an oncogene. Melanoma, for example, is caused by germline mutations of p16. The fact that each cell either had fully phosphorylated MAPK or none at all at the single cell level indicates that MAPK functions as a switch-like mechanism in every cell. The cell cycle is negatively controlled by cyclins, which activate the CDKs, and their inhibitors, or CDKIs, which depress the CDKs. Acute lymphocytic leukemia (ALL), soft-tissue sarcomas, bladder malignancies, glioblastomas, carcinoma pancreas, and non-small-cell lung carcinomas (NSCLC) are all brought on by somatically acquired p16 inactivation or deletion.

KEYWORDS: Cell cycle checkpoints, p53 gene, CDK proteins, MAPK, Non-small-cell lung carcinomas (NSCLC).

I. INTRODUCTION

A newly formed cell's cell cycle is a genetically controlled set of events that include the replacement of ions, growth, and division to produce two daughter cells. There are two phases in the process: the cell cycle (stage 1) and cell division (phase 2), which are a short dividing mitotic phase (M-phase) and a long non-dividing interphase (I-phase) [1]. The fundamental building blocks of all living things are cells, which give plants their leaves, roots, stalks, and flowers as well as their single cell structure and ongoing regulating division. In animals, cells are in charge of the bones, muscles, skin, and blood. The cells must procreate as the organism develops.

The series of internal processes a cell goes through to duplicate its genome and produce its other constituents is known as the cell cycle.Among these are the replication of its organelles and DNA, followed by the division of its cytoplasm and other constituents into two daughter cells. Prokaryotic and eukaryotic cells go through a similar cell cycle, however eukaryotic cells have a more complicated cell cycle. The word "cell cycle" describes the series of activities that occur inside a cell, such as growth and division.

The process by which a mother cell splits into two or more daughter cells is known as cell division. Growth, repair, and reproduction all depend on cell division. Cellular replications are the common term used to describe cell division.

II. THE STAGES OF THE CELL CYCLE

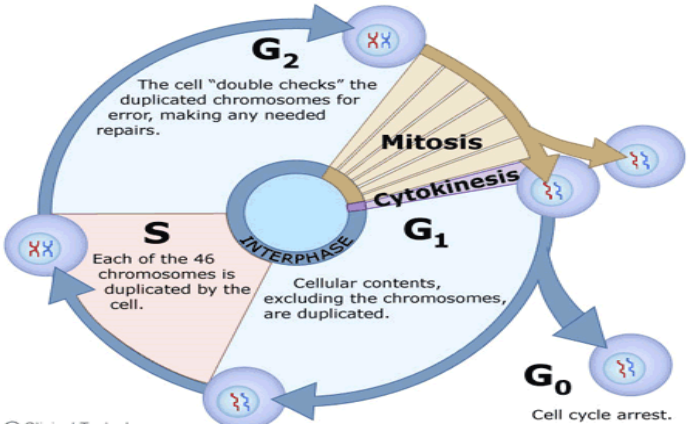
The two primary stages of the cell cycle process—the interphase and the mitotic phase—occur concurrently during cell division, particularly during mitosis.

A. **Interphase-** In the meantime, the cell is getting ready to divide by going through both cell growth and DNA replication in a systematic way during the interphase, which is also known as the resting phase. Approximately 95% of the cell cycle is spent in interphase. In Interphase, a freshly created cell and its nucleus enquiring a series of modifications before it becomes capable of dividing again. It is separated into four stages as well:

1. **G0 Phase (Quiescent stage)-** Cells in this phase do not divide, yet they continue to be metabolically active. In the reversible G0 phase, a cell can re-enter the cell cycle and divide; cells in this phase have distinct regulators that guarantee the cell's correct operation. Due to a lack of growth hormones or nutrition, cells may occasionally move from the checkpoint in the G1 phase into the G0 phase. Examples of cells that enter the G0 phase upon reaching maturity include muscle and nerve cells. Certain cells, such as the parenchymal cells of the liver and kidneys, can be made to divide by inducing them to enter the G0 phase semi-permanently (Figure 1).
2. **G1 phase (Gap 1)-** It is referred to as the first growth phase or post-mitotic gap phase because it is a component of the interphase, marks the end of the preceding mitotic phase, and lasts until DNA replication begins. All three sets of RNA, including mRNA, tRNA, and rRNA, have complete transcriptions, proteins are generated, and the cell is metabolically active and constantly expanding. Additionally, the length of the G1 phase varies greatly from cell to cell. The G1/S checkpoint determines the significance of the G1 phase. To ensure that the cell has the necessary resources to divide, procedures such as measuring nutrient concentration and DNA damage are carried out at this stage (Figure 1).
3. **S-Phase (Synthetic Phase)-** In order to create chromatin and chromatids, DNA replication occurs on the template of the preexisting DNA during the S-phase, sometimes referred to as the synthesis phase, which occurs between the G1 and G2 phases. Since the freshly replicated DNA molecules require histone proteins to form nucleosomes, protein formation—particularly histone protein formation—is crucial during this period. The G1/S checkpoint controls the entry into the S phase, allowing only cells with sufficient nutrition and sound DNA to proceed to the

following stage. It makes up over 30% of the entire cell cycle period and is rather lengthy. There are duplicate sets of genes on each chromosome. A haploid cell becomes diploid, and a diploid cell becomes tetraploid at the end of the S phase (Figure 1).

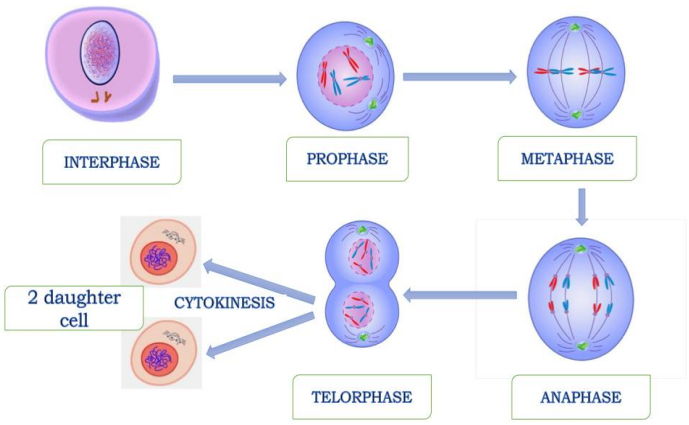
4. **G2 Phase (Gap 2)-** Because the cell releases proteins and gathers nutrients to get ready for the M phase, the G2 phase is also referred to as the second growth phase or pre-mitotic gap phase. In order to ensure that the cell is in a suitable state for division, this phase basically checks for DNA damage (during replication). It also controls the synthesis of proteins, RNAs, and DNA, stopping when it ceases [2]. This phase is when organelles and spindle formation begin, and the G2 checkpoint, which involves various proteins and complexes, controls the cell's transition from the G2 phase to the M phase. The cell stays in the G2 phase and is not passed for cell division if there is damage to the DNA or if there are not enough nutrients (Figure 1).



B. M Phase (Mitotic Phase)- The most dramatic multi-step process during which real cell division takes place is the mitotic phase. The contraction and relaxation of spindle fibers, which begin from centrioles and separate to form a double cell structure with an actual number of chromosomes, causes the chromosomes to travel quickly from the center to the poles during this phase. This stage begins with nuclear division, which is equivalent to the daughter chromosome's separation (Karyokinesis), and typically concludes with cytoplasmic division (Cytokinesis). Because the number of chromosomes in the parent and daughter cells stays the same, it is also known as an equational division (Figure 2).

The cellular division is called somatic division. Cell division results in the construction of diploid cells for growth and development. Karyokinesis and cytokinesis are the two main events that occur during mitosis in plants, which occurs in both haploid and diploid cells. The process of mitosis is carried out while the organism grows and develops. There are four stages to the Karyokinesis process:

1. Prophase- The chromosomes get thicker and shorter at this initial stage of mitosis, and they are easily visible. Pairs of chromatids become similar to chromosomes. The centrioles start to separate and go to opposing poles once the sister chromatids connect at a tiny central area known as the centromere. The achromatic spindle is formed by spindle fibers that emerge in the center of daughter centrioles. The nucleolus and nuclear membrane also disappear from this location, and other cell organelles like the Golgi complex and endoplasmic reticulum are absent during this stage (Figure 2)

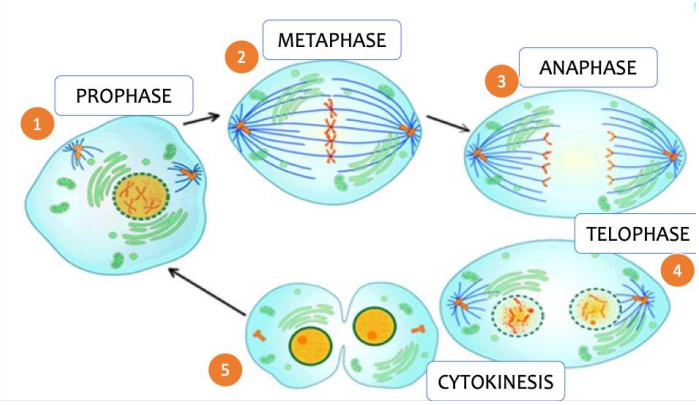


2. *Metaphase-* Each chromosome's centromere attaches to the spindle fibers at this phase. Both chromatids in every chromosome are attached to the spindle fiber from the opposing poles. At the equator, chromosomes align in a single plane. The metaphase plate is the plane where the chromosomes align during this phase (Figure 2).

3. *Anaphase-* It splits the centromere that connects the two chromatids. Each chromosome's two sister chromatids split off and are tugged in opposite directions by the shortening of spindle fibers. The divided chromosomes go in different directions to their poles. Anaphase stage is the name given to this stage (Figure 2).

4. *Telophase*- The spindle fibers disappear from view as the two sets of daughter chromosomes arrive at opposing poles. when spindle fibers start to fade. It caused a nuclear membrane to form surrounding the split chromosome clusters. The nucleolus, Golgi complex, and endoplasmic reticulum are among the other cell organelles that are created. Within the animal cell, the cleavage lines start to get deeper. Cytokinesis comes after Karyokinesis (Figure 2).

C. Cytokinesis- An invagination that starts in the middle of the cell membrane during the late telophase deepens and ultimately divides the cytoplasm into two halves, creating two new cells. The creation of the cell plate in the center of plant cells initiates the formation of the cell wall. The cytoplasm is divided into two halves as a result of this growing outward to meet the preexisting lateral walls. The plant cells' central lamellae are formed by this cell plate [3]. Some organisms, like fungus, algae, and plant cells, have cytokinesis that is not immediately followed by karyokinesis. As a result, a multinucleate stage known as a syncytium is produced. Although it happens in slightly different ways in plant and animal cells, the cytokinesis process occurs in both (Figure 3 and 4).



i. **Animal cytokinesis-** The spindle charges into the mid body, a thick, vesicular, fibrous structure on the equator. Microfilaments begin to accumulate in the center of the cell, causing the cell membrane to invade, a furrow to form, deepen centripetally, and ultimately the parent cell to split into two daughter cells. The cleavage method is the name given to this cytokinesis technique. Every cell organelle, including the Golgi complex, mitochondria, lysosomes, ER, ribosomes, and others, is likewise split almost evenly between the two daughter cells (Figure 3).

ii. **Plant cytokinesis**- The existence of a stiff cell wall distinguishes plant cytokinesis from animal cytokinesis. Cytokinesis is carried out by the cell plate method in higher plants and by cleavages in lower plants (like animal cells). At the equator, tiny Golgi complex vesicles are gathered during plant cytokinesis. Here, a spindle known as a phragmoplast endures for a while.

Every vesicle unites to produce two sheets that envelop a matrix or film that solidifies to form the middle lamella or cell plate. It develops centrifugally before the phragmoplasts eventually vanish. On either side of the cell plate, cellulose, hemicelluloses, and pectin are deposited. The major wall is formed by it (Figure 4).

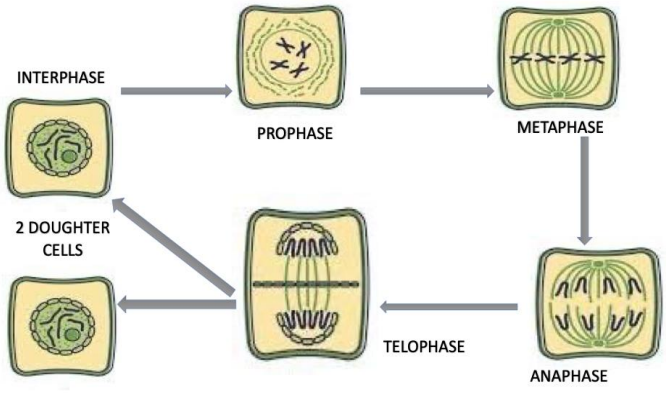


Figure 4- Cytokinesis in plant cells.

III. CELL CYCLE CHECKPOINTS

In both the prokaryotic and eukaryotic cell cycles, cell cycle checkpoints are regulating systems that guarantee appropriate progression. Along the cell cycle, each checkpoint functions as a possible termination point [4], where the cell's conditions are evaluated. Only when favorable conditions are satisfied does the cell go through the different phases of the cell cycle. The G1 checkpoint, sometimes referred to as the start or restriction checkpoints, is one of the three main checkpoints in the cell cycle [5]. The spindle checkpoints are another name for the metaphase-to-anaphase transition [6]. Progress through these checkpoints is mostly due to the activation of cyclin-dependent kinases by regulatory protein components named cyclins, which are produced at each stage of the cell cycle to govern the specific events that occur there [7]. There are several distinct versions of the protein cyclins, including cyclin A, B, D, and E. Each cyclin regulates the cell cycle at a distinct interphase phase (Figure 5).

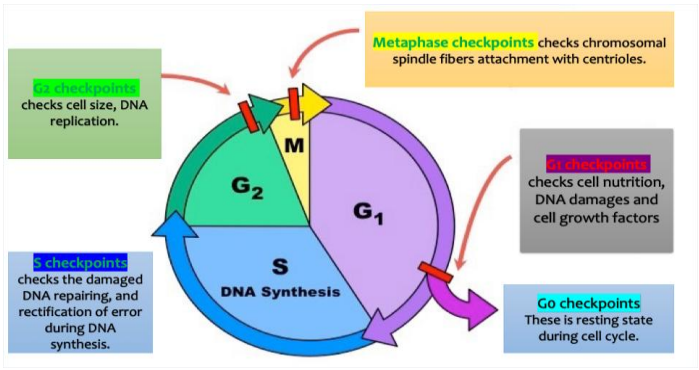


Figure 5: Cell Cycle Checkpoints at every stage during cell division.

1. G1 checkpoints

The start point in yeast and the restriction point in mammalian cells are other names for the G1 checkpoint. Depending on internal and external factors, the cell advances through G1, the stage at which it commits to entering the cell cycle. G1 checkpoints have the ability to either move past the restriction points or delay G1 and G0. Additionally, the G1 checkpoint controls cell size, nutrition, growth hormones, and DNA damage repair. The primary sign that a cell is restricting and not entering the cell cycle is DNA damage [8]. When cyclin-CDK-dependent transcription is activated, the cell decides to enter S phase and commit to a new round of cell division. The next step is guaranteed by this checkpoint [9] (Figure 5).There are two checkpoint work at G1 phase by its different mechanisms.

a. **MAPK signaling cascade**- Three pocket proteins, which are transcriptional repressors, bind to E2F transcription factors in the early stages of G1. These genes are members of a class of transcription factors that target numerous genes necessary for cell cycle regulation, such as CDKs, cyclins, checkpoint regulators, and DNA repair proteins. The E2F family is crucial for the strict control of DNA replication and division, as evidenced by the frequent discovery of E2F family dysregulation in cancer cases. To stop advancement past the G1 checkpoint, the three pocket proteins—retinoblastoma (Rb), p107, and p130—bind to E2F transcription factors. Proteins in this gene family have repressor and activator mechanisms, respectively.P107 and p130 co-repress these transcriptional factors, but E2F 4 and E2F 5 limit the transcription of G1-to-S promoting proteins. The activating E2F proteins, E2F 1, E2F 2, and E2F 3, are bound and repressed by the third pocket protein, Rb [9] (Figure 5).

b. **Cyclin-dependent kinase inhibitor 1B (CDKN1B)**- Cyclin-dependent kinase inhibitor 1B (CDKN1B), commonly referred to as p27 proteins, attaches to cyclins E, stops them from activating, and stops Cdk2 from acting. On the other hand, p27 protein activity is inhibited as Cyclin A builds up and binds to Cdk2. In order to fully activate Cyclin A: Cdk2, a complex that phosphorylates E2F 1-3 and causes them to dissociate from the DNA promoter sites, the G1 phase

cyclin-dependent kinase collaborates with the S phase cyclin-dependent kinase to target p27 for destruction [10]. As a result, E2F 6-8 can attach to DNA and prevent transcription. Another crucial mechanism that cells use to guarantee unidirectional movement and no reversals throughout the cell cycle is the negative feedback loop that effectively inhibits the inhibitor, p27 [11].

When DNA damage occurs, the cell detects any defects that need delaying and terminating the cell cycle in the G1 phase, which leads to arrest. Phosphorylation processes that start with either kinase ATM (Ataxia Telangiectasia mutated) or ATR (Ataxia Telangiectasia and rad3 linked) are part of the fast response. Depending on the kind of damage, both serve as sensors [12]. The effector kinases Chk-2 and Chk-1 are phosphorylated and activated by these kinases, respectively. By eliminating inhibitory phosphates from CDK2, Cdc25A promotes the cyclin E-CDK2 complex that was previously mentioned.

c. **P53 activity both in G1 and S phase**- One regulatory transcription factor protein that is commonly changed in human malignancies is the p53. It is also known as cellular tumor antigen p53, tumor protein P53, or transformation-related protein 53 (TRP53). Because of their function in maintaining stability by avoiding genome mutation, the p53 proteins are essential in vertebrates, where they defend the genome and prevent the development of cancer [13]. Thus, TP5 is categorized as a gene that suppresses tumors [14, 15]. To maintain the arrest, Chk1 or Chk2 phosphorylates the tumor suppressor p53. This stabilizes p53 by keeping it from joining Mdm2, a ubiquitin ligase that decreases p53 by directing it toward death. A number of target genes, including p21, an inhibitor of the G1-to-S promoting complex cyclin E-CDK2, are subsequently transcriptionally activated by the stable p53 [16]. Furthermore, the increase of p16 in response to DNA damage is another method by which p21 is triggered [17]. When cyclin D-CDK4 complexes are disrupted by the p16 gene, p21 is released from the complexes. This dephosphorylates and activates Rb, enabling Rb to bind and inhibit E2F 1-3 and prevent the cell from entering S phase. Aspects of this paradigm have been contested recently [15].

1. G2 checkpoints

G2 goes through a DNA damage checkpoint, same like S Phase. The cell is inspected again for areas of incomplete replication or damaged DNA. Both ATM and ATR kinases are drawn to areas of damage. Along with p53 activation, Chk1 and Chk2 activation also occurs to cause cell cycle arrest and stop the progression into mitosis. Cyclin B-Cdk1 phosphorylation is required to deactivate the Pre-Replicative Complex (Pre-RC), another element of S phase [6].

a. Cyclin-dependent kinase 2-

The enzyme cyclin-dependent kinase 2, also known as cell division protein kinase 2 (Cdk2), is encoded by the human CDK-2 gene [18]. The protein is a cyclin-dependent kinase that is a member of the Ser/Thr protein kinase family. The gene products of S. cerevisiae cdc28 and S. pombe cdc2, which are also referred to as Cdk1 in humans, are fairly similar to this kinase. The cyclin-dependent kinase complex's catalytic component is only active during the G1–S phase of the cell cycle, when cells duplicate their DNA and produce the proteins required for mitosis.

The complex's regulatory subunits, such as cyclin E or A, bind to and control this protein. While connecting with Cyclin A is necessary to advance through the S phase, Cyclin E binds G1 phase Cdk2, which is necessary for the transition from G1 to S phase [19]. Phosphorylation also controls its action. This gene has been found to contain numerous transcriptions beginning sites and alternatively spliced variants [20].

The process by which G2 protein accumulation activates cyclin B in CDK-1. CyclinA-Cdk2 deactivates the cyclinB-Cdk1 inhibitor Wee1 by activating Cdc25, an activator of cyclinB-Cdk1. As a result, cyclin B expression and Cdk1 activation are greatly increased, creating a positive feedback loop. The kinase Plk1 phosphorylates Wee1 when the cell advances through G2 and reaches the G2/M transition, directing Wee1 for destruction by the SCF ubiquitin ligase complex [21]. Phosphorylation of Cdc25 is another way that Plk1 activates it. Cdc2 is activated when Wee1 degradation and Cdc25 activation work together to remove inhibitory phosphorylation from cdc2. The G2/M transition is where Plk1 is activated. They build up and create an activation complex during G2.

Cdc2 is then further activated by a positive feedback loop initiated by the Plk1-Cdc2-cdc25 complex. The resulting cdc2-cyclin B complexes activate downstream receptors that promote mitotic entry when cyclin B levels increase during G2. The G2/M transition gene Mem1-Fkh is likewise activated by the resulting Cdk1 activity. Since M phase initiation is an all-or-nothing event that engages in hysteresis, a sharp increase in cyclin B-Cdk1 activity is required. By creating a minimum threshold of cyclin B concentration, cyclin B-mediated hysteresis of Cdk1 activity propels M phase entry. This protects the all-or-nothing event by existing at a level above the minimal required for the continuation of the M phase following entry. Incomplete DNA replication raises this entrance concentration even more, introducing a second regulatory mechanism at the G2/M transition point. As a result of cyclin B-Cdk1 activity, hysteresis enables highly controlled M phase entry [22].

b. G2–M transition in Xenopus oocytes

To understand how the G2-M transition into mitosis is regulated, The cell enters mitosis at the conclusion of G2, during which the nucleus splits. An all-or-nothing effect and irreversibility characterize the dramatic G2 to M shift. Since entering mitosis is a crucial stage in a cell's life cycle, this is beneficial to the cell. The cell would experience numerous problems with partially dividing if it did not fully commit, which would probably result in the cell's death [23]. When progesterone attaches to a membrane-bound receptor in frog oocytes, the signal cascade is activated. Mos is triggered downstream. After then, MEK1 is phosphorylated by Mos, phosphorylating MAPK. MAPK has two functions: Mos is activated and the CyclinB-Cdk1 complex is activated to start mitosis. Mos functions as a toggle switch to create the all-or-nothing entrance into mitosis because its activation results in a positive feedback loop.

c. Activity of MAPK-P (phosphorylated MAPK)-

By demonstrating that MAPK-P (phosphorylated MAPK) concentrations rose in response to rising progesterone levels, this feedback loop was initially discovered. The fact that each cell either had fully phosphorylated MAPK or none at all at the single cell level indicates that MAPK functions as a switch-like mechanism in every cell. Furthermore, it was demonstrated that inhibiting Mos protein synthesis results in more graded MAPK-P responses, indicating that Mos protein synthesis is essential for the all-or-none nature of MAPK

activation (Figure 6).

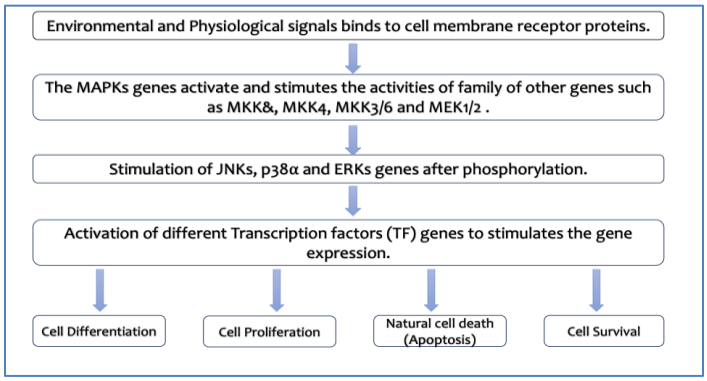


Figure 6- flow diagram of MAPKs genes and transcription factors (TF) on the gene expression that stimulates the proliferation, differentiation, apoptosis and survival of cells.

IV. REPLICATION STRESS RESPONSE

It makes sense that mechanisms would be in place to prevent an early entry into mitosis, given that it represents a significant and expensive commitment for the cell. It has been demonstrated that errors in earlier stages, like having unreplicated DNA segments, prevent the cell cycle from progressing. According to the Novak-Tyson model, this happens via increasing the amount of cyclin B required for mitotic entry.

Sha et al. (2003) examined Xenopus egg extracts to see if this was the case. To inhibit DNA polymerase and stop DNA replication, they employed aphidicolin (APH) [23]. As expected by the Novak–Tyson model, the threshold of activation rose to 80–100 nM when Cyclin B was administered during interphase. The dynamic link between cyclin and MPF in interphase arrest in frogs of the Xenopus species was discovered and described by Bela Novak and John Tyson in 1990 [24]. P34cdc2 cyclin activation and cyclin breakdown in the interphase of cdc 2 kinases' amphibian eggs [25, 26]. Thus, these studies demonstrate that the hysteresis loop is impacted by the stress of unreplicated DNA in the cell, which raises the cyclin B threshold for mitotic entry.

V. METAPHASE CHECKPOINTS

The mitotic spindle checkpoints occur during the metaphase stage of cell division when all of the centrosomes are aligned at the mitotic plate and under bipolar strain. The anaphase entry is brought on by the sensed tension that results from this bipolar connection. The sensing mechanism ensures that the anaphase-promoting compound (APC/C) is no longer obstructed in order to achieve this. This allows it to breakdown cyclin B, which has a D-box (destruction box), and securin, which in turn slows separase, that cuts cohesins, the protein composite that holds sister chromatids together. After this inhibitory protein has been broken down by ubiquitination and subsequent proteolysis, separase causes sister chromatid separation. Upon dividing into its two daughter cells, the cell reaches G1 (Figure 9).

Pds1p (securin) controls the cohesion of sister chromatids in S. cerevisiae when the onset of anaphase is initiated because it binds to and inhibits the protease Esp1p, sometimes referred to as separin or separase. The anaphase-promoting chemical (APC). This anaphase-promoting compound that degrades securin is referred to as a cyclosome. A ring E3 ubiquitin ligase recruits an E2 ubiquitin-conjugating enzyme loaded with ubiquitin. When securin, Cdc20, and E2 are all linked to APC/C, E2 ubiquitinates securin and carefully eliminates it. Esp1p/separase, a protease released by securin degradation, rips away the cohesin rings which link sister chromatids together in order to promote their separation [27].They also demonstrated that serine residues next to the cutting site for Scc1 are phosphorylated by Polo/Cdc5 kinase, which would promote the cutting action [28]. However, other studies demonstrate that as sister centromeres split apart and sister chromatids migrate toward the cell's poles, the cohesiveness of the arms eventually disappears [29, 30].

VI. CYCLIN'S ROLE IN CANCER: CDK COMPLEX

The uncontrolled and uncontrollable growth of cells is referred to as cancer or malignancy. The overexpression of cyclin D in cancers of the breast, esophagus, liver, and a subset of lymphomas is an illustration of how cell cycle regulator genes or checkpoint genes are either irregular or altered in cancer. However, CDK4 gene amplification is the cause of malignancies such glioblastomas, sarcomas, and melanomas [31]. Malignancies emerge as a result of unregulated cell proliferation spurred on by mutations in the genes encoding cell-cycle regulatory proteins and in the regulation of the cell cycle [32, 33].

As a result, it has been proposed that one promising method of treating malignancies is to use therapeutic drugs to alter the activity of these proteins [34]. The fact that each cell either had fully phosphorylated MAPK or none at all at the single cell level indicates that MAPK functions as a switch-like mechanism in every cell. The cell cycle is adversely affected by cyclins, which stimulate the CDKs, and their drugs, or CDKIs, which depress the CDKs. In many cancers of humans, the CDKIs are frequently repressed or mutated [35]. For example, melanoma is caused by p16 mutations which are inherited. Bladder cancers, glioblastomas, esophageal cancer, acute lymphocytic leukemia (ALL), non-small-cell lung carcinomas (NSCLC), soft-tissue sarcomas, and cancers of the pancreas are all driven on by somatically acquired p16 inactivation or deletion [31, 22]. While an oncogene is a gene that, when mutated, acquires a function or is overexpressed, converting a normal cell into a cancer cell, a proto-oncogene is a normal gene that has the potential to transform into an oncogene through mutations [36]. Additionally, it induces kinases to increase gene transcription. The proto-oncogene functions normally when there is an overabundance of cyclins in the cells, which causes the body to go through a regular cell cycle. However, it also inhibits the p53 gene, which stops natural cell death.

The tumor suppressor gene, the second significant gene, acts antagonistically against proto-oncogenes. It boosts the p53 gene, which encourages natural cell death, and suppresses the cyclin molecules, which trigger the cell cycle in a limited way. These kinases, known as transcription factors, typically impact the G1/S transition, leading to a decrease in inhibition and an increase in cyclin-CDK expression at an inappropriate cell cycle stage [37, 38] (Figure 7).

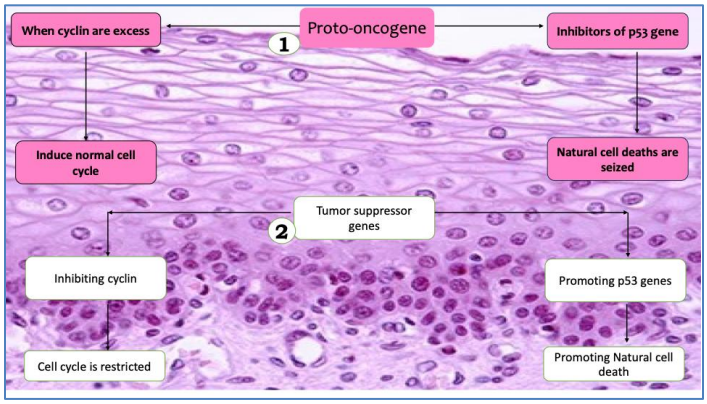


Figure 7- Proto-oncogene and tumor suppressor gene flow diagram.

VII. DISCUSSION

The G1 checkpoint is one of the three primary checkpoints in the cell cycle and is sometimes known as the start or restriction checkpoints [5]. Two G1 checkpoints are the MAPK signaling cascade and the cyclin-dependent kinase inhibitor 1B (CDKN1B). Cdk2 and cyclin-A form a complex that inhibits the activity of the p27 protein, resulting in the inhibition of Cdk2 activity and the activation of cyclin E. In the interphase of amphibian eggs containing cdc 2 kinases, P34cdc2 cyclin activation and cyclin breakdown occur [25, 26]. The stress of unreplicated DNA in the cell, which increases the cyclin B threshold for mitotic entry, is therefore shown to affect the hysteresis loop in these investigations.

Depending on both internal and external factors, the cell advances through G1, which is sometimes referred to as the restriction point at which it commits to beginning the cell cycle. The primary sign that a cell is restricting and not entering the cell cycle is DNA damage [8]. The G1 phase cyclin-dependent kinase works with the S phase cyclin-dependent kinase to target p27 for destruction in order to completely activate Cyclin A: Cdk2, a complex that phosphorylates E2F 1-3 and causes them to detach from the DNA promoter sites [10]. During early G1, three pocket proteins—transcriptional repressors—attach to E2F transcription factors. These genes belong to a class of transcription factors that target many genes essential for the regulation of the cell cycle, including checkpoint regulators, cyclins, DNA repair proteins, and CDKs.

To understand how the G2-M transition into mitosis is regulated, The cell enters mitosis at the conclusion of G2, during which the nucleus splits. An all-or-nothing effect and irreversibility characterize the dramatic G2 to M shift. Since entering mitosis is a crucial stage in a cell's life cycle, this is beneficial to the cell.

The anaphase-promoting complex (APC/C) can now degrade cyclin B, which possesses a D-box (destruction box), securin, and separase, which therefore degrades cohesins, the protein composite that holds sister chromatids together.

The fundamental idea and contributing elements of the cell cycle checkpoint are covered in this paper. Cell division and cell cycle checkpoints are regulated by a number of interrelated variables. Through the cell cycle program, which in turn sends signals that change the oscillation of CDK activity so as to further control the cell cycle events, these checkpoint factors operate and control the cell cycle and division of cells process in a regular and controlled way. There are still certain parts of checkpoint signaling that are unclear, either as the fundamental idea or in relation to illnesses. Cell division is controlled and regulated by a number of checkpoint factors, including MAPK, CDK, p53, cyclin-dependent kinase-2, and cyclin-dependent kinase inhibitors 1B, which operate at distinct stages of the cell cycle, including G0-, G1-, S-, and M-phase. These elements are in charge of keeping healthy cells from developing into cancerous ones. Unquestionably, an ever-expanding collection of extremely advanced experimental instruments and methodologies may be used to further investigate the hidden facets of checkpoint signaling, giving us a clearer and more comprehensive view of the cell cycle's extraordinary fidelity.

The unrestrained and uncontrollable proliferation of cells is known as cancer or malignancy. because cancers of the breast, esophagus, liver, and a subgroup of lymphomas produce too much cyclin D. On the other hand, cancers such glioblastomas, sarcomas, and melanomas are caused by CDK4 gene amplification [31]. Mutations in the genes encoding cell-cycle regulatory proteins and in the regulation of the cell cycle cause unchecked cell proliferation, which in turn leads to the development of malignancies [32, 33]. As a result, it has been proposed that one promising method of treating malignancies is to use therapeutic drugs to alter the activity of these proteins [34].

The fact that each cell either had fully phosphorylated MAPK or none at all at the single cell level suggests that MAPK functions as a switch-like mechanism in every cell. The cell cycle is adversely affected by cyclins, which stimulate the CDKs, and their inhibitors, or CDKIs, which depress the CDKs. In many human cancers, the CDKIs are frequently repressed or mutated [35]. For example, melanoma is caused by p16 mutations which are inherited. Mutations in the p16 gene cause bladder malignancies, soft-tissue sarcomas, pancreatic carcinoma malignancy, glioblastoma, non-small cell lung cancer, and acute lymphocytic leukemia [31, 22]. An active oncogene results in an overexpression of the gene, transforming a healthy cell into a malignant one. A normal gene that can be transformed into an oncogene is referred to as a proto-oncogene [36]. It also stimulates kinases to boost the transcription of genes. When the body experiences a regular cell cycle due to an excess of cyclins in the cells, the proto-oncogene operates normally. But it also prevents spontaneous cell death by inhibiting the p53 gene.

The second important gene that opposes proto-oncogenes is the tumor suppressor gene. It suppresses the cyclin molecules, which partially initiate the cell cycle, and increases the p53 gene, which promotes spontaneous cell death. We have covered the basics of cell cycle checkpoints and how they function to control and regulate the cell division process since they are crucial and govern the regular cell division process in organisms.

Certain cell cycle checkpoints can detect abnormalities and communicate with other healthy cells to fix them. The body develops cancer at that particular spot from the malignancy if all of these cell abnormalities that have already developed are not corrected. Thus, the cell cycle checkpoints are essential for regulating the growth of unwanted cells (malignancy) within the body of an organism [39].

ACKNOWLEDGMENTS

Author thanks to Dr. Santosh Kumar Tripathi sir Principal, Marwar Business School, Gorakhpur for stimulating and support for this work and provide important document and platform to write this article. We thanks to our colleagues and collaborator for their support.

CONFLICT OF INTEREST

Author has no conflict of interest.

VII. REFERENCES

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